Tetracyclic Phenothiazines. VII (1). Electron Impact Promoted Mass Spectral Fragmentation of Some Pyrido[3,2,1-*kl*]phenothiazines

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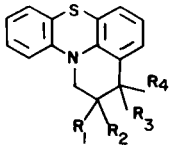
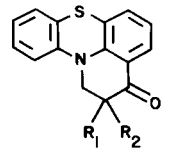
Received January 8, 1982

The mass spectral fragmentation pattern of a series of pyrido[3,2,1-*kl*]phenothiazines is reported. The major fragments are derived from the breakdown of the pyrido ring and substituents thereon. The 1,2-/2,3-unsaturated, unsubstituted and most of the 3-substituted compounds show the molecular ion as the base peak indicative of their relative stability toward electron impact. The genesis of the base peaks from the molecular ions of the 2,2-dithiophenyl substituted compounds probably involves a concerted expulsion of a neutral diphenyldisulfide molecule and hydrogen atom transfer from the 1-position to the 2-position in the pyrido ring. On the other hand, 2-thiophenyl substituted molecular ions lead to base peaks involving simultaneous ring opening of the pyrido ring, cleavage of phenylthiomethylene moiety as a radical and contractive ring closure to the pyrrole system. These two mechanisms appear to be diagnostic for distinguishing 2,3- versus 2,2-positional isomers. The McLafferty rearrangement takes place in the 2-thiophenyl and 2,2-dithiophenyl substituted compounds. The retro-Diels-Alder fragmentation of the pyrido ring occurs in varying degrees depending on the nature of the 2- and 3- substituents and also the presence or absence of unsaturation in the pyrido ring. In the 2-thiophenyl-3-keto compounds, thiophenyl group participation with 3-carbonyl carbon and oxygen atoms is observed in the genesis of some interesting ion fragments. The detection of metastable ions in the spectra of 1,2-dihydro-2-thiophenyl-, 1,2-dihydro-2,2-dithiophenyl-3-hydroxy-, and 1,2-dihydro-2,2-dithiophenyl-3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazines; and spectra of 1,2-dihydro-3-methyl-, 1,2-dihydro-2-carbethoxy-3-keto- and 1,2-dihydro-2-thiophenyl-3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazines at low voltage support major fragmentation pathways.

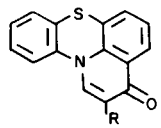
J. Heterocyclic Chem., **19**, 849 (1982).



Cpd	R1	R2	R3	R4
1	H	H	H	H
2	H	H	H	CH_3
3	H	H	H	C_6H_5
4	H	H	H	OH
5	H	H	D	OH
6	H	SC_6H_5	H	OH
7	H	SC_6H_5	H	SC_6H_5
8	H	SC_6H_5	H	H
9	SC_6H_5	SC_6H_5	H	H
10	SC_6H_5	SC_6H_5	H	OH
11	SC_6H_5	SC_6H_5	D	OH

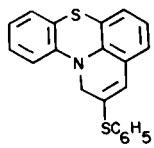


Cpd	R1	R2
12	H	H
13	H	$COOC_2H_5$
14	H	SC_6H_5
15	SC_6H_5	SC_6H_5



16 R=H

17 R=SC_6H_5



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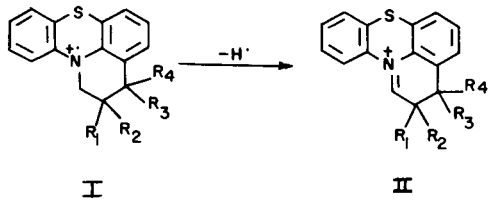
In our program directed toward the synthesis of conformationally restricted tetracyclic phenothiazine tranquilizers (2,3), we have obtained numerous pyrido[3,2,1-*kl*]-phenothiazine derivatives as potential intermediate or side products. Our investigation of the mass spectra of these compounds revealed interesting relationships between the substitution pattern in their pyrido ring and the fragmentation pathways. Although the mass spectra of phenothiazine based drugs and some other derivatives (4-9) and the parent phenothiazine itself (10) have been systematically investigated, to our knowledge no attempt has yet been made to study mass spectra of pyrido-[3,2,1-*kl*]phenothiazine derivatives. This report describes the mass spectral fragmentation patterns of the 2-, 3-, 2,2-and 2,3-substituted pyrido[3,2,1-*kl*]phenothiazines.

Duffield, Craig and Kray (5) have reported the stability of certain tricyclic phenothiazines toward electron impact by observing doubly charged species of the respective molecular ions. In our observations this stability is extended to pyridophenothiazines **1, 2, 4, 12, 16** and **17**, which in conjunction with the observed doubly charged molecular ion peaks of weak to moderate intensities also exhibit singly charged molecular ions as the base peaks.

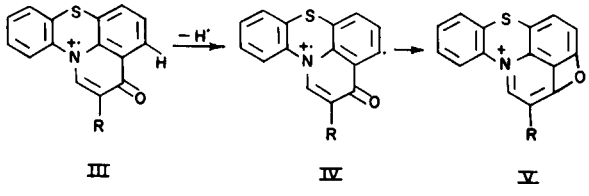
Compounds **6, 8, 10, 14** and **15** do not show M-1 peaks. However, compounds **1-5, 9, 11, 12** and **13** do show M-1 peak forming characteristic pyridinium ion (11) [resulting from loss of a hydrogen atom from the 1-position], the in-

tensities of which vary from 49.5% to 0.2% of their respective base peaks depending on the substituents (Scheme 1). The comparatively greater intensity of M-1 ions peaks observed for 3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**16**) and 2-thiophenyl-3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**17**) can be attributed to formation of a stable planar (12) fused oxetenium ion V as shown in Scheme 2. This explanation is further supported by the observation that the M-1 ion is not observed in the spectrum of 1,2-dihydro-2-thiophenyl-3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**14**)

Scheme 1



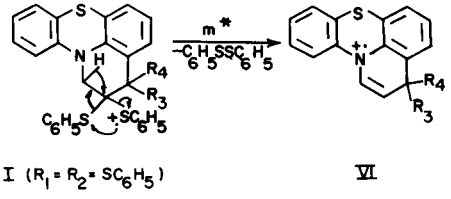
Scheme 2



and the daughter ions corresponding to compounds **16** and **17**, derived from their parent ions corresponding to **14** and **15**, respectively do show relatively intense M-1 peaks.

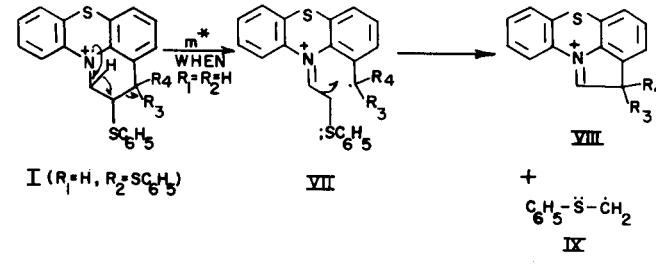
The base peaks of 2,2-dithiophenyl substituted compounds **9-11** and **15** appear to be generated in a concerted fashion as shown in Scheme 3. This one-step fragmentation was confirmed by the detection of metastable ions for the daughter ions of **10** and **15**.

Scheme 3



A feasible general mechanism is proposed in Scheme 4 for the fragmentation of the 1,2-dihydro-2-thiophenyl-3*H*-pyrido[3,2,1-*kl*]phenothiazines **6**, **7**, **8** and **14** leading to the genesis of base peaks VIII in most of these cases. The driving force for this process apparently is the formation of the benzylically stabilized (5) imminium radical ion VII resulting from ubiquitous cleavage (13) of α,β C-C bond next to S, and the stable thiophenyl methylene radical IX (14). Expulsion of the latter, accompanied by concerted contractive ring closure gives stable pyrrolidinium ion VIII. This mechanism also is predominant in fragmentation of compound **13** with substituent other than thiophenyl at the 2-position leading to the generation of respective major peaks by loss of neutral species and stable radicals. Compound **7** (although present in a mixture together with **8** and **18**) nonetheless also exhibited a

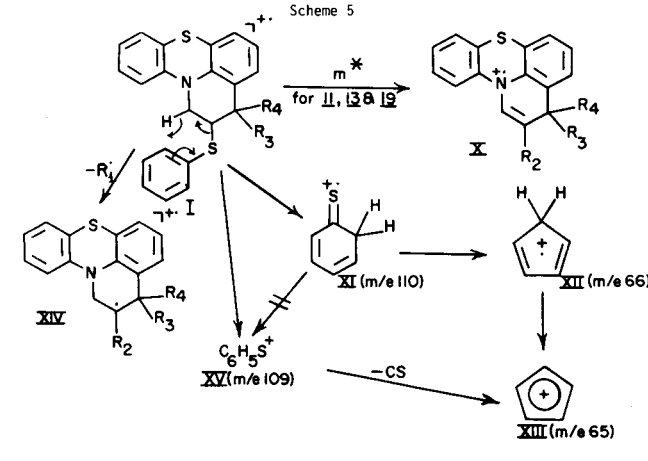
Scheme 4



reasonably intense peak corresponding to VIII (R_3 = H, R_4 = SC_6H_5, m/e 332) consistent with the proposed general mechanism. It is noteworthy that the mechanisms shown in Schemes 3 and 4 are useful to distinguish the positional isomers **7** and **9**. In fact, the spectrum of compound **9** does not show a peak at m/e 332. This result suggests that the fragmentation of 2,2-dithiophenyl compounds, in general, does not follow the mechanism shown in Scheme 4 to any important extent.

The other important feature as shown in Scheme 5, in the dissociation of molecular ions of 3-thiophenyl- and 2,2-dithiophenyl-3*H*-pyrido[3,2,1-*kl*]phenothiazines, **8** and **9**, is the McLafferty rearrangement as observed by Bieman (15) in other systems. The importance of this process is governed by the stability of the resultant ion X. The

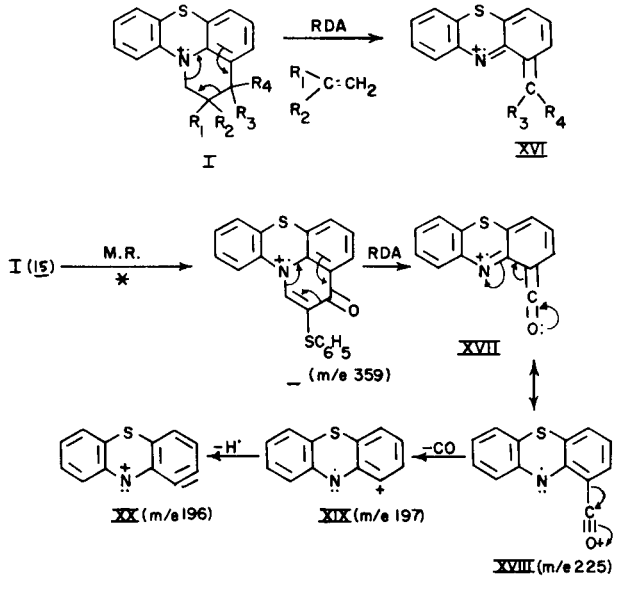
Scheme 5



molecular ion I (R_2 = SC_6H_5) also dissociates to ions XIV and XV (m/e 109) due to cleavage of one of the C-S bonds. The mass spectrum of compound **14** at lower ionizing voltage clearly shows that: (a) the ratio of the abundances of m/e 251: m/e 252, corresponding to ions X and XIV, remains virtually constant at 35 eV (16) and 70 eV indicating that the species of mass m/e 251 arises directly from the molecular ion I (**14**) and not from ion m/e 252 by loss of a hydrogen atom; and (b) the constant ratio of the abundances of m/e 109 (XV); m/e 110 (XI) likewise demonstrates that XV does not arise from XI by loss of a hydrogen atom, but is instead derived directly from the molecular ion I (**14**). That the molecular ions of compounds **8, 10** and **15** exhibit metastable peaks at m/e 162 (Calcd. 161.8), m/e 277 (Calcd. 276.7) and m/e 274.8 (Calcd. 274.8) for their daughter ions X at m/e 237 (11.5%), m/e 361 (5.1%) and m/e 359 (80.2%), respectively, confirms the McLafferty rearrangement process. The ion X of mass m/e 362 observed in the spectrum of C-3 deuterated compound **11** with the retention of the deuterium atom further supports this conclusion.

The relative abundance of retro-Diels-Alder fragment ions XVI, derived from breakdown of the pyrido ring (Scheme 6), depends on the nature of substituents at the 2-and 3-positions. Unsaturation in the pyrido ring makes this process so facile that the 1,2-saturated molecular ion I (**15**), instead of taking a direct route of retro-Diels-Alder fragmentation, undergoes McLafferty rearrangement to give an ion of mass m/e 359 corresponding to **17**. The latter, in turn, undergoes retro-Diels-Alder fragmentation to ion XVII. Ion XVII then further fragments to XIX and XX due to subsequent losses of CO and a hydrogen atom.

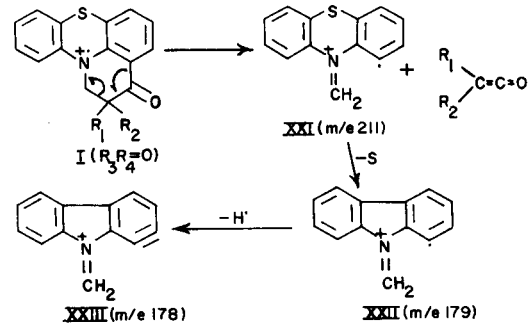
Scheme 6



The importance of this process, which is relatively common in 3-keto-substituted compounds, depends on the nature of C-2 and C-3 substituents. The fact that pyrido-[3,2,1-*kl*]phenothiazine (**16**), an aromatic compound, does not give the retro-Diels-Alder fragment ion XVII could be attributed to much greater stability of its molecular ion.

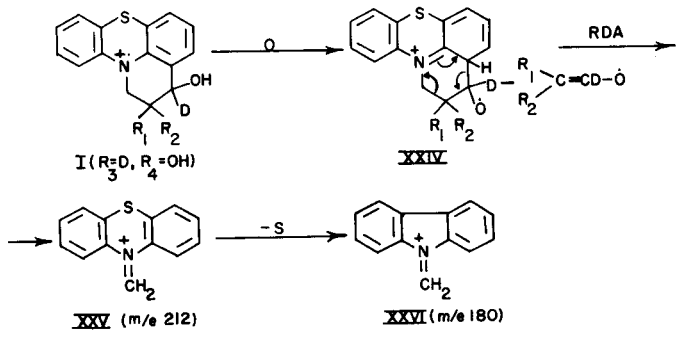
The 1,2-dihydro-2-substituted ketones also appear to lose a neutral ketene or substituted ketene molecule (Scheme 7), leading to a stable radical ion XXI (m/e 211) that further loses an S atom to give ion XXII (m/e 179). The comparatively low intensities of XXI and XXII indicate that this process is of minor importance. In some cases the XXIII also has been observed as a very low intensity ion.

Scheme 7



In the mass spectra of 3-hydroxy, 3-methyl and 3-phenyl compounds (**3-5, 10,** and **11**) the retro-Diels-Alder fragmentation leading to ion XXV (m/e 212), Scheme 8, normally observed in spectra of *N*-alkyl-substituted phenothiazines due to facile cleavage of α,β C-C bond next to N, also takes place after an initial hydrogen atom transfer to phenothiazine ring at C-1 position by simple cleavage of the O-H, C-H of the CH_3, or C-H of the C_6H_5 group bond. The ion XXV then loses S atom to give ion XXVI (m/e 180). That the C_3-H bond does not break is confirmed by deuterium labelling at this position in compounds **5** and **11**. The hydrogen atom transfer from side chain to 1-position in phenothiazine ring is also reported (7) in simpler

Scheme 8

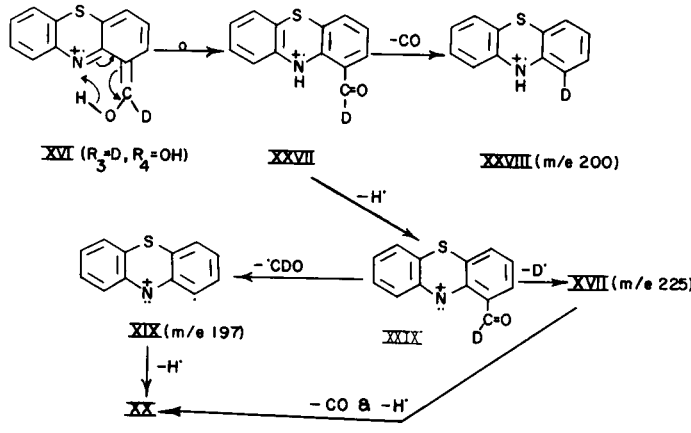


systems. In the mass spectrum of the C-3 deuterated compound **11**, a similar retro-Diels-Alder fragmentation followed by subsequent cleavages is observed only after the molecular ion I (**11**, m/e 472) has undergone McLafferty rearrangement (Scheme 5).

The enolic ion XVI (R_3 = D, R_4 = OH) (Scheme 9) ketonizes through a six-membered transition state transferring its hydroxyl hydrogen atom to N giving the rearranged ion XXVII (m/e 228). This ion further dissociates to XXVIII by loss of CO and to XXIX by loss of a hydrogen atom. XXIX then loses a deuterium atom to give XVIII and ·CDO radical to afford ion XIX. Ion XX may arise from XIX by loss of a hydrogen atom or from XVII by loss of a neutral CO molecule and a hydrogen atom.

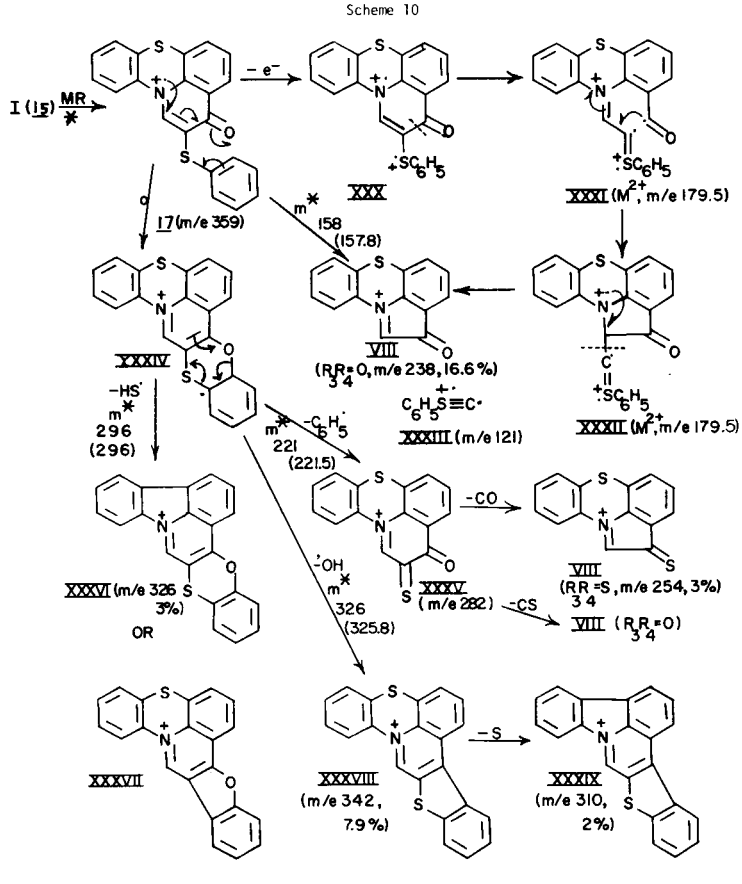
Neighboring group participation of the thiophenyl group with the carbonyl carbon and oxygen atoms in the molecular ions of 2-mono and 2,2-dithiophenyl-3-keto-substituted compounds **14**, **15** and **17** is evidenced by certain common fragment ions observed in their mass spectra (see Scheme 10 for the spectrum of **15** as a representative example). Thus, the ion corresponding to **17** apparently rearranges to hexacyclic ion XXXIV which could lose a

Scheme 9



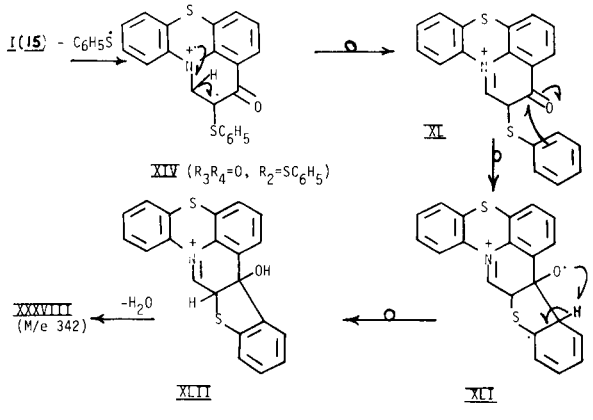
phenyl radical through retro-Diels-Alder process in the thioxane ring leading to ion XXXV (m/e 282). The fact that the ion XXXV has very weak intensity (< 1%) can be explained by its facile loss of either of CS to give VIII (R_3,R_4

Scheme 10



= O) or of CO to yield VIII (R_3,R_4 = S, m/e 254, 3%). Additionally, cleavage of the molecular ion to yield ions XXXIII (m/e 121) and VIII (R_3,R_4 = O) through a sequence of doubly charged species XXX, XXXI and XXXII (m/e 179.5) apparently also occurs. Thus VIII (R_3,R_4 = O) may potentially arise by three different routes. Ion XXXIV also loses hydrogen sulfide radical to give either of the ions XXXVI or XXXVII of m/e 326 (3%). Ion XXXIV also dissociates by loss of a hydroxyl radical to yield ion XXXVIII (m/e 342, 7.9%) which most likely loses S atom from the phenothiazine ring to give ion XXXIX (m/e 310, 2%). Contribution to the ion XXXVIII (m/e 342) also appears to derive from the ion XIV (R_3,R_4 = O, R_2 = SC_6H_5, m/e 360) as shown in Scheme 11. This process apparently involves participation of thiophenyl ring with the carbonyl carbon causing formation of the rearranged ions XL, XLI and XLII to eventually form XXXVIII (m/e 342)

SCHEME II



by loss of a water molecule. Although the daughter ions reported in Schemes 10 and 11 for which metastable ions have been observed have relative abundance of usually less than 10%, the chain of facile rearrangements involving and yielding fused hexacyclic species is nonetheless interesting.

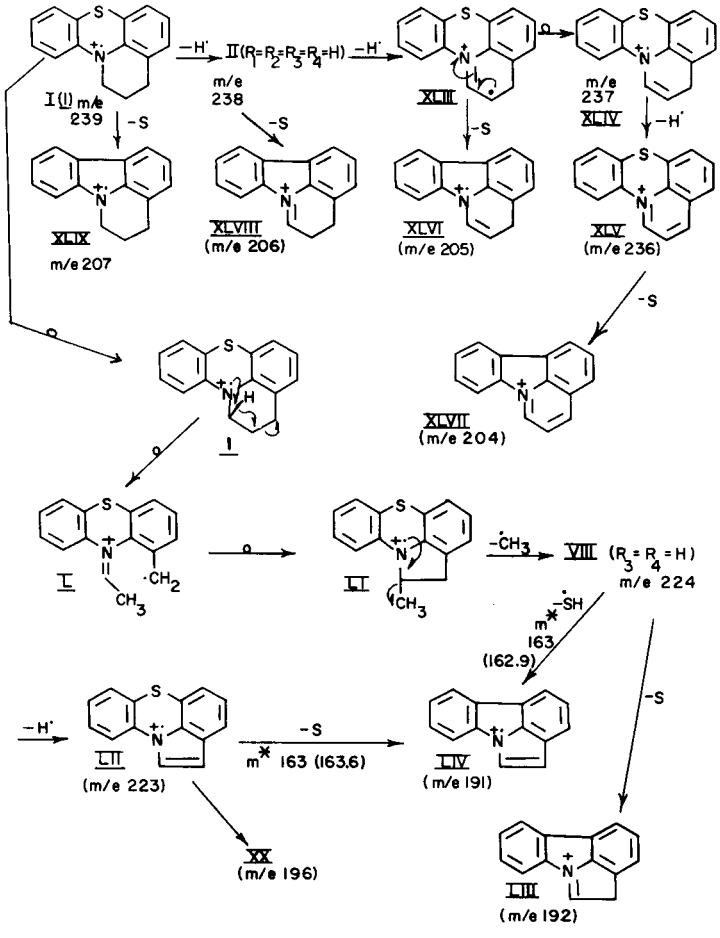
Other fragment ions observed in the mass spectra of almost all the tetracyclic compounds in the series are characteristic of the substituents such as methyl, phenyl, methoxy, hydroxy, ester and keto groups. The genesis of the common fragment ions is depicted in Schemes 12-15. Most of these pathways are supported by low ionizing voltage studies (5) of compounds (**2**, **13** and **14**); metastable ion studies of compounds (**8**, **10** and **15**); and deuterium labelling studies of compounds (**5** and **11**). Stable molecular ions that give rise to doubly charged ions, lose the S atom from the phenothiazine moiety directly to yield M-32 ions such as LXX. The unsaturated ketones give M-28 ions due to loss of CO molecule, albeit of low abundance, such as LII. Successive loss of hydrogen radicals from the molecular ions occurs until the pyrido ring acquires aromaticity as in XLV. The resultant ions also lose S atom giving rise to ions such as XLIX, XLVIII, XLVI and XLVII. That the ion XLIX does not lead to the ions XLVIII, XLVI and XLVII by successive loss of hydrogen radicals is evidenced in the spectrum of compound **2** (M^+ = 253) wherein constant ratios of the abundances of m/e 220:221; 205:206; and 204:205 at 35 eV and 70 eV are observed (5). The molecular ion (**1**) follows two successive rearrangements, possibly through L to LI, which by loss of a methyl radical, generates VIII (R_3 = R_4

Table 1

Compound No.	Molecular Formula	Mp (°C)	% C	% H	% N
6	$C_{21}H_{17}NOS_2$	100-130 (a)	69.17 (69.42) (b)	4.87 (4.69)	3.86 (3.86)
8	$C_{21}H_{17}NS_2$	158-159	72.86 (72.62)	4.92 (4.90)	4.01 (4.02)
9	$C_{27}H_{21}NS_3$	184-185	71.11 (71.21)	4.56 (4.62)	3.37 (3.08)
10	$C_{27}H_{21}NOS_3$	169-170	68.71 (68.79)	4.66 (4.46)	2.80 (2.97)
14	$C_{21}H_{15}NOS_2$	162-163	69.44 (69.80)	4.23 (4.16)	3.77 (3.88)
15	$C_{27}H_{19}NOS_3$	181-182	68.94 (69.08)	4.02 (4.05)	3.03 (2.98)
17	$C_{21}H_{13}NOS_2$	168-169	67.69 (67.52)	3.95 (4.35)	3.99 (3.58)
18	$C_{21}H_{15}NS_2$	138-139	73.33 (73.04)	4.39 (4.35)	3.88 (4.06)

(a) This is a mixture of *erythro* and *threo* diastereomers. (b) All calculated values are given in parentheses.

Scheme 12

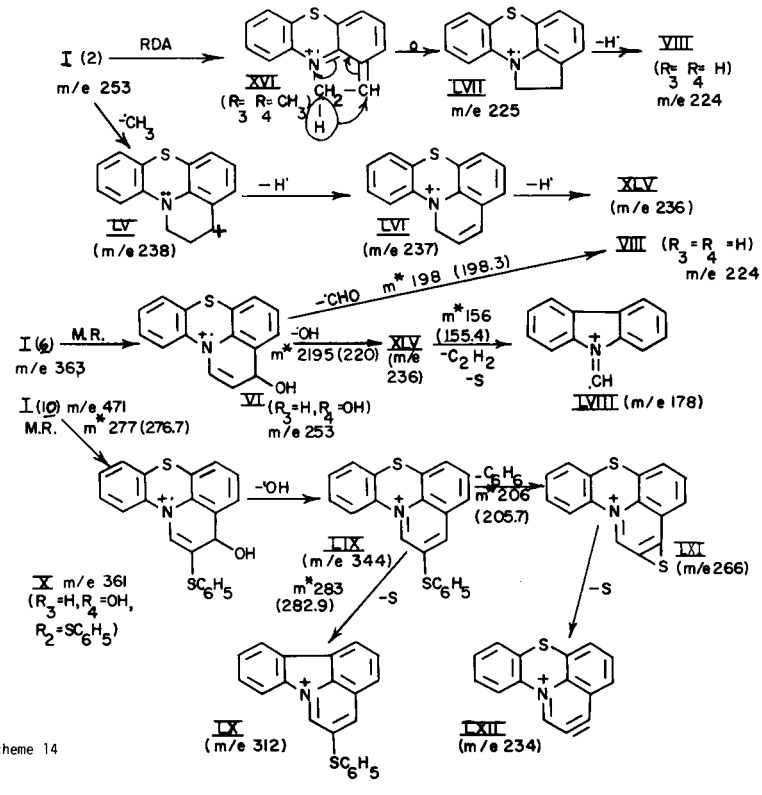


= H). This ion then loses hydrogen atom resulting to LII which further dissociates by loss of C_2H_3 moiety to give XX and by loss of S to give LIV. Part of the contribution of LIV comes from VIII (R_3 = R_4 = H) by loss of a ·SH radical. The structure of the ion LIV gains support from a fragmentation pattern identical to the one observed in the mass spectrum of parent pyrrolophenothiazine (17-19) itself. Again at two different ionizing voltages (5,16), the constant ratio of the abundance of m/e 191:192 supports the conclusion that ion LIV is derived from VIII (R_3 = R_4 = H) and not from LIII.

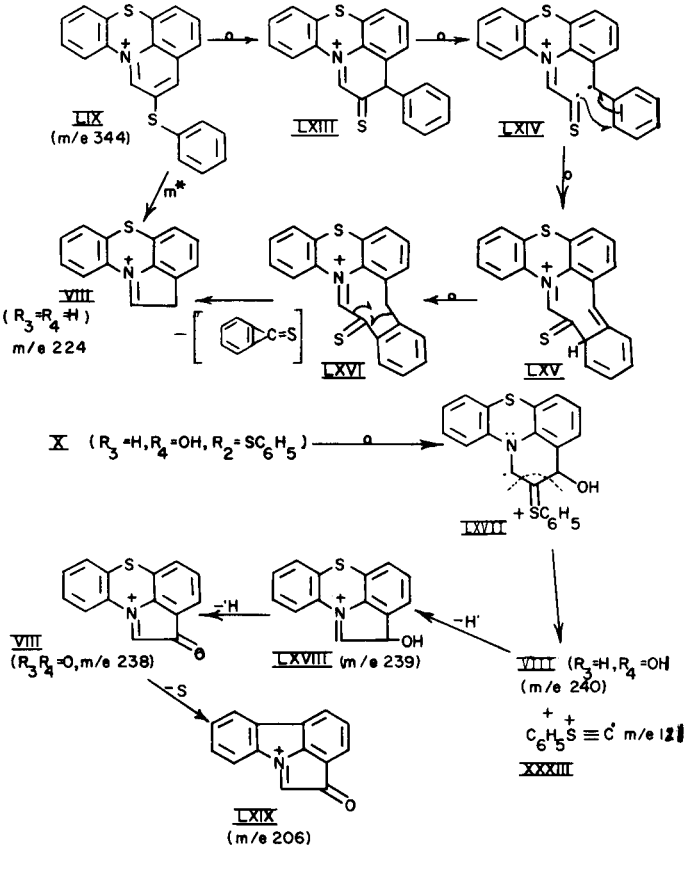
The molecular ions (**2, 3-5**) lose the C-3 substituent to give the benzylically stabilized cation LV which further suffers two successive losses of hydrogen atoms to give LVI and XLV (Scheme 13). The ion LVII (m/e 225) derived by rearrangement of the retro-Diels-Alder fragment ion XVI (R_3 = H, R_4 = CH_3) from I (**2**, m/e 253) loses a hydrogen atom to give VIII (R_3 = R_4 = H, m/e 224). The McLafferty rearrangement ion VI (R_3 = H, R_4 = OH, m/e 253) from I (**6**) through loss of the ·CHO radical gives VIII (R_3 = R_4 = H). Loss of ·OH radical from VI (R_3 = H, R_4 = OH) gives XLV which, in turn, loses acetylene and an S atom to give the ion LVIII (m/e 178). These processes are supported by metastable ion studies. Likewise, the McLafferty rearrangement ion X from I (**10**) through loss of hydroxyl radical gives the ion LIX (m/e 344), an identical species to the one generated from the molecular ion of the compound **18**, fragments further through two metastable ion-supported routes. Thus, ion LIX loses benzene to give LXI (m/e 266) and by loss of S atom gives LX (m/e 312). Ion LXI also loses S atom to give the interesting hetaryne ion LXII (m/e 234).

Ion LIX (m/e 344) also gives VIII (R_3 = R_4 = H) by loss of C_7H_4S either directly or through a convenient sequence of rearranged ions LXIII → LXIV → LXV → LXVI possibly involving at least two [1,3]-sigmatropic shifts (Scheme 14). The overall process is supported by metastable ion studies. Also the ion X derived from I (**10**) probably rearranges to LXVII which further dissociates to VIII (R_3 = H, R_4 = OH, m/e 240) and XXXIII (m/e 121). The ion VIII (R_3 = H, R_4 = OH, m/e 240) through two successive losses of hydrogen atoms goes to VIII (R_3,R_4 = O, m/e 238). The ion VIII (R_3,R_4 = O) loses an S atom to give LXIX (m/e 206). Ion VI (R_3,R_4 = O, m/e 251), the base peak of **15** formed directly from the molecular ion, dissociates in two major ways (Scheme 15) as evidenced by

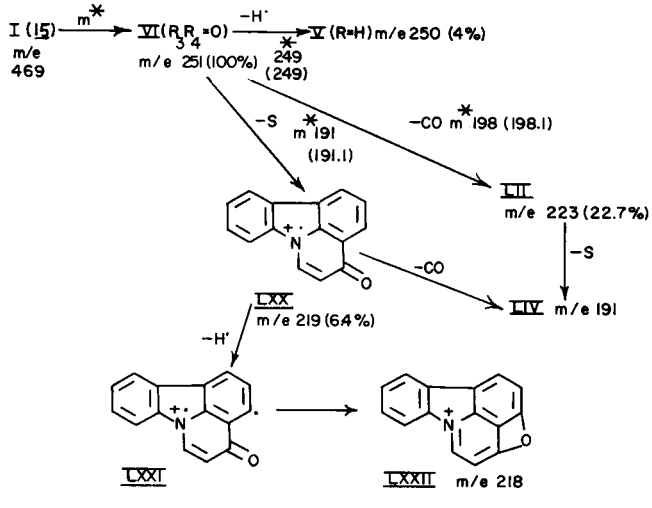
Scheme 13



Scheme 14



Scheme 15



metastable ions leading to LII by loss of CO and to LXX by loss of an S atom. These ions, in turn, lose S atom and CO respectively to give the common ion LIV (m/e 191). It is interesting to note the loss of a hydrogen atom from the ion LXX (m/e 219), a characteristic process normally observed in the spectra of unsaturated carbonyl compounds **20** and **21**.

From the study of the mass spectra of these compounds it can be concluded that the initial major fragmentations occur in the pyrido ring leaving phenothiazine moiety intact. It is hoped that these spectra will be useful for elucidation of fragmentation pathways for more complex structures to be prepared in this laboratory and possibly also for identification of metabolites of future phenothiazine based drugs.

EXPERIMENTAL

The mass spectra were recorded on a Varian MAT 311A double focusing mass spectrometer at 70 eV. The mass spectra of compounds **2, 13** and **14** were also recorded on low ionizing voltage at 35 eV. The samples were introduced by direct inlet probe and were heated at a rate of about 450° in 200 seconds. The metastable ion spectra were obtained by focusing on the parent ion and scanning the electrostatic sector and magnetic field at a rate such that the ratio E/B remained constant at a constant accelerating voltage. All the compounds, except 1,2-dihydro-2,3-dithiophenyl-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**7**), used in this investigation were of analytical purity. Microanalyses were performed by the University Analytical Center, Tucson, Arizona, USA. Compounds **1-3** (20), **4** (21), **12** (22), **13** (23) and **16** (24) are reported in the literature. The preparation of compounds **6-10** (25) and **14, 15, 17** and **18** (26) will be reported separately. The calculated metastable peaks are listed in parentheses under individual schemes. The relative abundance of ions below 2% have been ignored unless they were of particular interest.

1,2-Dihydro-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**1**).

This compound was prepared (25) by reduction of 1,2-dihydro-3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**12**) with aliminum hydride (alane) and had mp 55-56° [lit (20) mp 55-56°]; ms: m/e (%) 239 (M^+, 100), 238 (49.5), 237 (4.6), 236 (10.7), 224 (34), 223 (25.5), 222 (5), 212 (14.9), 211 (93.4), 210 (33.3), 209 (5), 208 (5.5), 207 (24.9), 206 (52), 205 (19), 204 (31), 191 (10), 184 (4), 179 (6), 178 (7.5), 167 (11.7), 166 (6), 152 (5), 119.5 (12.3), 112 (6), 111.5 (16), 106 (6.4), 105.5 (29), 105 (10), 77 (7), 76 (6), 69 (10), 63 (10).

1,2-Dihydro-3-methyl-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**2**).

This compound was prepared by us (20) and had mp 88-89°; ms: m/e (%) 253 (M^+, 100), 252 (11), 240 (4.6), 239 (14.5), 238 (78), 237 (8.7), 236 (14.7), 225 (18.8), 224 (16), 223 (31.6), 212 (2), 211 (4), 210 (4), 206 (11), 205 (21.7), 204 (26.8), 192 (4), 191 (6.9), 126.5 (M^{2+}, 16.5), 119 (9), 118.5 (11), 118 (10), 112.5 (14.3), 112 (8.7), 111.5 (42.8), 106 (6), 105.5 (6), 102 (9), 69 (16.6).

The mass spectrum of compound **2** was also recorded at 35 eV; ms: m/e (%) 255 (M + 2, 6), 254 (M + 1, 18.4), 253 (M^+, 100), 252 (3.6), 240 (1.5), 239 (4.8), 238 (26), 237 (3.7), 236 (7), 225 (7), 224 (6.6), 223 (13.7), 211 (1.5), 210 (1.7), 206 (4.5), 205 (8.6), 204 (12.2), 192 (1.9), 191 (2.9), 126.5 (4), 119 (1.8), 112.5 (2.9), 111.5 (3.6).

1,2-Dihydro-3-phenyl-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**3**).

This compound was prepared by us (20) and had mp 162°; ms: m/e (%) 317 (M + 2, 9.4), 316 (M + 1, 29.6), 315 (M^+, 100), 314 (5.1), 286 (10.4), 236 (8.4), 224 (1.6), 223 (5.3), 212 (1.1), 211 (4.3), 204 (6.7), 78 (5.7), 77 (3).

1,2-Dihydro-3-hydroxy-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**4**).

This compound was prepared in quantitative yield by reduction of 1,2-dihydro-3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**12**) with excess sodium borohydride in 3:1 mixture of tetrahydrofuran and methanol. It had mp 124-125° [lit (21) mp 124-125°]; ms: m/e (%) 257 (M + 2, 6.2), 256 (M + 1, 16.9), 255 (M^+, 100), 254 (2.4), 238 (5.7), 237 (4.2), 236 (12.2), 227 (5.5), 226 (1.6), 225 (0.7), 224 (0.9), 223 (2.3), 212 (2), 211 (1.9), 210 (0.9), 204 (3.6), 199 (2.9), 198 (2.9), 197 (1.7), 167 (3.6), 127.5 (M^{2+}, 1.5), 119 (2.5), 118.5 (4.5), 77 (1.6), 69 (2), 65 (0.8), 55 (1.3).

1,2-Dihydro-3-hydroxy-3D-pyrido[3,2,1-*kl*]phenothiazine (**5**).

This compound was prepared in the same manner as compound **4** by reduction of the ketone **12** with equivalent amount of sodium borotetradeuteride. The desired compound **5** was purified by preparative tlc eluting with methylene chloride. It had mp 124-125° [lit (21) mp 124-125°], the same as the non-deuterated compound **4**; ms: m/e (%) 258 (M + 2, 7.7), 257 (M + 1, 24), 256 (M^+, 100), 255 (11.4), 239 (6), 238 (5), 237 (12), 228 (6.5), 212 (1.5), 207 (1.2), 206 (3), 205 (3.8), 200 (2.4), 199 (2.3), 198 (2.5), 168 (3.5), 167 (2.2), 128 (M^{2+}, 2.1), 119 (5), 77 (1.5), 75 (1), 69 (2).

1,2-Dihydro-2-thiophenyl-3-hydroxy-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**6**) (25).

This compound had mp 100-130° (mixture of *erythro*- and *threo*-diastereomers); ms: m/e (%) 365 (M + 2, 6.1), 364 (M + 1, 12.2), 363 (M^+, 49.8), 361 (0.4), 347 (0.3), 346 (0.5), 345 (1.6), 344 (1.2), 312 (0.4), 254 (2), 253 (4.8), 252 (4.5), 251 (1.7), 242 (6.1), 241 (16.5), 240 (100), 239 (5.8), 238 (4.9), 237 (12.5), 236 (29.1), 235 (3.1), 227 (2.1), 226 (2.6), 225 (15.1), 224 (13.5), 223 (15.5), 214 (1.6), 213 (4.6), 212 (27.7), 204 (13), 199 (4.8), 198 (5.1), 197 (3.8), 191 (4.4), 180 (4.4), 178 (1), 168 (2.7), 167 (9.6), 162 (18.3), 123 (1.5), 110 (14.2), 109 (7.5), 106 (7), 105 (28.8), 102 (6.4), 95.5 (5), 91 (4), 90 (2.5), 89 (5.8), 77 (13.5), 76 (4.6), 69 (7.9), 66 (10), 65 (9.5), 63 (9.7), 57 (6), 52 (5.9).

Anal. Calcd. for $C_{21}H_{17}NOS_2$: C, 69.42; H, 4.69; N, 3.86. Found: C, 69.17; H, 4.87; N, 3.86.

1,2-Dihydro-2-thiophenyl-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**8**) (25).

This compound had mp 158-159°; ms: m/e (%) 349 (M + 2, 6.1), 348 (M + 1, 12.7), 347 (M^+, 52.1), 238 (13.1), 237 (11.5), 236 (20.6), 226 (7.1), 225 (20.9), 224 (100), 223 (24.4), 206 (3.2), 205 (5), 204 (12.5), 191 (2.5), 178 (1.1), 123 (0.2), 109 (2.4), 77 (2.4), 69 (2.9), 65 (2.8).

Anal. Calcd. for $C_{21}H_{17}NS_2$: C, 72.62; H, 4.90; N, 4.02. Found: C, 72.86; H, 4.92; N, 4.01.

1,2-Dihydro-2,2-dithiophenyl-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**9**) (25).

This compound had mp 184-185°; ms: m/e (%) 457 (M + 2, 8.6), 456 (M + 1, 15.5), 455 (M^+, 46.6), 454 (0.3), 347 (2.7), 346 (6.3), 345 (13.5), 344 (9), 254 (2), 253 (8.4), 252 (4.7), 239 (8), 238 (25.8), 237 (100), 236 (79.5), 235 (5.4), 234 (5.2), 224 (7.6), 223 (5.3), 205 (2.1), 204 (10.5), 123 (6.2), 110 (7.7), 109 (5), 91 (1.5), 77 (3.7), 66 (3.5), 65 (6.7).

Anal. Calcd. for $C_{27}H_{21}NS_3$: C, 71.21; H, 4.62; N, 3.08. Found: C, 71.11; H, 4.56; N, 3.37.

1,2-Dihydro-2,2-dithiophenyl-3-hydroxy-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**10**) (25).

This compound had mp 169-170°; ms: m/e (%) 473 (M + 2, 12.7), 472 (M + 1, 22.4), 471 (M^+, 69.8), 364 (1.4), 363 (4.2), 362 (2.33), 361 (5.1), 360 (1.5), 359 (2.2), 346 (3.4), 345 (10.7), 344 (16.9), 312 (1), 266 (0.7), 255 (5.9), 254 (19.8), 253 (100), 252 (49.5), 251 (7), 240 (5.4), 239 (7.3), 238 (9.8), 237 (8.4), 236 (47.1), 235 (5.4), 234 (6.3), 227 (5.9), 226 (6), 225 (18.4), 224 (76.8), 223 (26.1), 222 (4), 220 (2), 210 (1), 204 (3.5), 203 (1), 199 (2), 198 (5.8), 197 (5.3), 196 (4.5), 191 (4.2), 178 (1), 167 (3.6), 166 (2), 123 (17.4), 110 (44.5), 109 (27.9), 91 (8.8), 84 (6), 77 (13), 69 (5.1), 66 (16.3), 65 (15.5), 51 (12.8).

Anal. Calcd. for $C_{27}H_{21}NOS_3$: C, 68.79; H, 4.46; N, 2.97. Found: C, 68.71; H, 4.66; N, 2.80.

1,2-Dihydro-2,2-dithiophenyl-3-hydroxy-3D-pyrido[3,2,1-*kl*]phenothiazine (**11**).

This compound was prepared by reduction of 1,2-dihydro-2,2-dithiophenyl-3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**15**) (25) with sodium borotetradeuteride in a 3:1 mixture of tetrahydrofuran and methanol. After usual work up, the product was purified by preparative tlc eluting with methylene chloride. It had mp 169-170° [lit (25) mp 169-170° for nondeuterated compound **10**]. There was no nmr signal for benzycylic methine hydrogen at δ 4.65 (25); ms: m/e (%): 474 (M + 2, 12.7), 473 (M + 1, 22.4), 472 (M^+, 69.8), 471 (10), 363 (2.3), 362 (5.1), 345 (16.9), 254 (100), 252 (49.5), 241 (5.4), 239 (7.3), 238 (9.8), 237 (47), 228 (5.9), 225 (18.4), 224 (27), 223 (20), 205 (3.5), 192 (3), 191 (3.6), 123 (12), 110 (11), 109

(11), 91 (5), 77 (5), 69 (5), 66 (4), 65 (8).

1,2-Dihydro-3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**12**).

This compound was prepared according to the literature procedure and had mp 113-114° [lit (22) mp 113°]; ms: m/e (%) 255 (M + 2, 6.2), 254 (M + 1, 17.3), 253 (M^+, 100), 252 (8.6), 251 (0.9), 225 (5.1), 224 (1.7), 223 (2.4), 219 (0.6), 212 (0.8), 211 (3.9), 197 (21.3), 196 (9.6), 193 (0.6), 192 (0.6), 191 (1.2), 165 (0.8), 126.5 (M^{2+}, 2.2), 112.5 (11.8).

1,2-Dihydro-2-carbethoxy-3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**13**).

This compound was prepared by us (22). It had mp 113°; ms: m/e (%) 327 (M + 2, 7.6), 326 (M + 1, 22.5), 325 (M^+, 100), 324 (0.7), 279 (40.4), 278 (4), 252 (39.2), 251 (5.5), 250 (0.8), 238 (2), 225 (13.6), 224 (3), 223 (7), 222 (4.5), 220 (2.1), 211 (0.6), 210 (0.7), 119 (1.4), 198 (4.4), 197 (17.9), 196 (7.9), 191 (2.2).

The mass spectrum of compound **13** was also recorded at 35 eV; m/e (%) 327 (M + 2, 10.1), 326 (M + 1, 29.4), 325 (M^+, 100), 324 (1), 281 (5.8), 280 (18), 279 (80.6), 278 (9.1), 255 (1.4), 254 (7.6), 253 (26.8), 252 (90.7), 251 (10.3), 250 (1.6), 238 (2), 236 (1.4), 227 (1.7), 226 (4.9), 225 (30.3), 224 (7.2), 223 (17.5), 222 (10.8), 221 (1.6), 220 (5.2), 219 (3), 212 (1.5), 211 (1.4), 210 (1.6), 199 (3), 198 (10), 197 (40.9), 196 (16.5), 191 (4.8), 180 (1.7), 177 (2), 171 (2), 169 (2).

1,2-Dihydro-2-thiophenyl-3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**14**) (26).

This compound had mp 162-163°; ms: m/e (%) 363 (M + 2, 15), 362 (M + 1, 31.2), 361 (M^+, 97.6), 359 (1.3), 254 (1.9), 253 (8.3), 252 (25.6), 251 (25.8), 250 (1), 240 (5.9), 239 (17.9), 238 (100), 225 (3.1), 224 (8.3), 223 (15.9), 222 (4.6), 220 (3.4), 219 (3.4), 198 (2.6), 197 (8.5), 196 (7.3), 191 (3.9), 123 (7), 110 (7.5), 109 (4), 77 (3.3), 69 (2), 66 (2.7), 65 (3.2).

The mass spectrum of this compound was also recorded at 35 eV; me (%) 363 (M + 2, 9.9), 362 (M + 1, 20.1), 361 (M^+, 80.9), 359 (2), 254 (2), 253 (7.3), 252 (28.2), 251 (41.6), 250 (2.1), 240 (6.1), 239 (16.6), 238 (100), 226 (1), 225 (3.7), 224 (10.4), 223 (24.4), 222 (6.7), 220 (5.2), 219 (5.4), 198 (3.4), 197 (10.1), 196 (8.5), 191 (6), 123 (8.4), 110 (2.6), 109 (2.8), 77 (1.2), 66 (1.2), 65 (1.4).

Anal. Calcd. for $C_{21}H_{15}NOS_2$: C, 69.80; H, 4.16; N, 3.88. Found: C, 69.44; H, 4.23; N, 3.77.

1,2-Dihydro-2,2-dithiophenyl-3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**15**) (26).

This compound had mp 181-182°; ms: m/e (%) 471 (M + 2, 9), 470 (M + 1, 15.8), 469 ($^+$, 49), 362 (2.8), 361 (12.5), 360 (23.4), 359 (80.2), 358 (5.2), 342 (7.9), 326 (3.1), 310 (1.9), 282 (0.1), 254 (3.2), 253 (12.3), 252 (30.3), 251 (100), 250 (4), 238 (16.6), 227 (1.9), 226 (6.6), 225 (24.9), 224 (4.6), 223 (22.7), 222 (11.1), 219 (6.4), 218 (1), 210 (1.5), 199 (2.5), 198 (7.6), 197 (39.4), 196 (16), 191 (6), 121 (10.2), 110 (12.1), 109 (7), 91 (3.7), 77 (5.4), 76 (1.7), 69 (9.4), 66 (5.6), 65 (6.3).

Anal. Calcd. for $C_{27}H_{19}NOS_3$: C, 69.08; H, 4.05; N, 2.98. Found: C, 68.94; H, 4.02; N, 3.03.

3-Keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**16**).

This compound was prepared by us (24) and had mp 206°; ms: m/e (%) 253 (M + 2, 6.7), 252 (M + 1, 18.5), 251 (M^+, 100), 250 (4.3), 223 (8), 222 (4.2), 219 (6.5), 203 (2.5), 197 (1.8), 196 (3.3), 191 (3.6), 125.5 (M^{2+}, 4.5). 111.5 (5.3), 69 (2.4).

2-Thiophenyl-3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (**17**) (26).

This compound had mp 168-169°; ms: m/e (%) 361 (M + 2, 13.1), 360 (M + 1, 27.9), 359 (M^+, 100), 358 (11.7), 343 (4.5), 342 (17.2), 326 (7.8), 310 (5.2), 294 (2.5), 282 (1.7), 254 (2.3), 253 (4.6), 252 (1.7), 249 (1.5), 240 (2), 239 (5), 238 (27.9), 227 (3.5), 226 (8.7), 225 (53.8), 223 (1.3), 222 (3), 221 (1.7), 199 (4.9), 198 (14.2), 197 (87.4), 196 (19.4), 179.5 (M^{2+}, 8.4), 163 (11), 121 (28.9), 105 (5.8), 89 (2.4), 77 (5.3), 76 (2.6), 69 (8.2), 65 (2.3), 51 (8.5).

Anal. Calcd. for $C_{21}H_{13}NOS_2$: C, 67.52; H, 4.35; N, 3.58. Found: C, 67.69; H, 3.95; N, 3.99.

1*H*-2-Thiophenylpyrido[3,2,1-*kl*]phenothiazine (**18**) (26).

This compound had mp 138-139°; ms: m/e (%) 347 (M + 2, 24.8), 346 (M + 1, 29.3), 345 (M^+, 100), 344 (70.8), 313 (4.1), 312 (13.6), 300 (6.5), 238 (4), 237 (8.4), 236 (35.8), 235 (13.1), 234 (16.4), 226 (2.2), 225 (6.8), 224 (36.3), 223 (19.2), 222 (3.8), 204 (9), 191 (4.8), 167 (5.3), 110 (16.1), 91 (0.8), 77 (2.8), 66 (6.5), 55 (7).

Anal. Calcd. for $C_{21}H_{15}NS_2$: C, 73.04; H, 4.35; N, 4.06. Found: C, 73.33; H, 4.39; N, 3.88.

Acknowledgement.

We thank the National Institute of Mental Health for support in the form of Research Grant No. MH 31184. We also thank Mr. Peter F. Baker for recording the mass spectra and Dr. K. H. Schram for helpful discussions.

REFERENCES AND NOTES

(1) L. C. Vishwakarma and A. R. Martin, *J. Heterocyclic Chem.*, **19**, 103 (1982).

(2) S. H. Kim and A. R. Martin, *ibid.*, **15**, 1507 (1978).

(3) A. R. Martin, S. H. Kim, H. Y. Yamamura and A. S. Horn, *J. Med. Chem.*, **23**, 938 (1980).

(4) R. Guedj, A. Cambon, L. Audier and M. Azzaro, *Bull. Soc. Chim. France*, 1022 (1968).

(5) A. M. Duffield, J. Cymerman Craig and L. R. Kray, *Tetrahedron*, **24**, 4267 (1968).

(6) J. N. T. Gilbert and B. J. Millard, *Org. Mass Spectrom.*, **2**, 17 (1969).

(7) J. Heiss and K. P. Zeller, *ibid.*, **2**, 819 (1969).

(8) A. P. Melikian, N. W. Flynn, F. Petty and J. D. Wander, *J. Pharm. Sci.*, **66**, 228 (1977).

(9) W. Riepe and M. Zander, *Z. Naturforsch A.*, **27**, 170 (1972); *Chem. Abstr.*, **76**, 105266p (1972).

(10) L. Audier, M. Azzaro, A. Cambon and R. Guedj, *Bull. Soc. Chim. France*, 1013 (1968).

(11) R. M. Silverstein, G. C. Bassler and T. C. Marill, "Spectrometric Identification of Organic Compounds", 3rd Ed, John Wiley and Sons, Inc, New York, 1974, p 32.

(12) S. I. Chen, J. Zinn and W. P. Gwinn, *J. Chem. Phys.*, **34**, 1319 (1969).

(13) R. I. Reed, "Applications of Mass Spectrometry to Organic Chemistry", U. S. Edition, Academic Press Inc, New York, 1966, p 110.

(14) H. Budzikiewicz, C. Djerassi and D. H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, Inc, San Francisco, 1967, p 288.

(15) K. Biemann, "Mass Spectrometry", McGraw-Hill, New York, 1962, pp 123-124.

(16) The spectrum run at 17 eV would have been the ideal one (5), however, it is equally informative at 35 eV as well.

(17) R. A. Hollins and A. C. Pinto, *J. Heterocyclic Chem.*, **15**, 711, (1978).

(18) A. Hallberg, D. Deardorff and A. R. Martin, *Heterocycles* **19**, 75 (1981).

(19) L. C. Vishwakarma, A. Hallberg and A. R. Martin, (Communicated).

(20) A. R. Martin, S. H. Kim, G. W. Peng, G. V. Siegel and T. J. Yale, *J. Heterocyclic Chem.*, **15**, 1331 (1978).

(21) E. F. Godefroi and E. L. White, *J. Org. Chem.*, **21**, 1163 (1956).

(22) N. L. Smith, *ibid.*, **15**, 1125 (1950).

(23) D. S. Huang, T. J. Yale and A. R. Martin, *J. Med. Chem.*, **12**, 705 (1969).

(24) A. R. Martin, G. G. Briggs and T. J. Yale, *J. Pharm. Sci.*, **57**, 166 (1968).

(25) L. C. Vishwakarma, V. M. Paradkar, A. R. Martin and C. J. Grol, *Heterocycles*, in press.

(26) L. C. Vishwakarma, A. R. Martin and C. J. Grol, (Unpublished results).